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GROUP 120

PATENT
Case 2328IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

: Art Unit: 123

Elijah H. Gold et al

: Examiner: D. Phillips
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sioner of Patents and Trademarks, Washington, D.C.
20231, on 11/4/85
(Date of Deposit)

For Patent for:

Angiotensin-Converting Enzyme
Inhibitors

Serial No.: 635,390

Anita W. Magatti
Registered Representative

Filed: July 30, 1984

Anita W. Magatti
Signature

11/4/85

Date of Signature

Schering-Plough Corporation
Madison, New Jersey 07940Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

RESPONSE AFTER FINAL REJECTION

This is in response to the Final Rejection mailed
September 5, 1985, in which claims 1-30 were rejected and claim
31 was withdrawn from consideration under 37 C.F.R 1.142(b).

Claims 1-30 are rejected under 35 U.S.C. 103 as being
obvious over the Hoefle et al and Vincent et al patents. The
rejection states that

"[t]he Hoefle et al patent indicates that
the alanyl substituted condensed ring
nitrogen containing one carboxyl ring
system has anti-hypertensive activity. It
also establishes that the sulfur
substitution would be expected to be
equivalent... to the alanyl substituted
ring. ...[T]here is adequate basis in the
references to make the combination... [T]he
art does provide basis for the substitution
of the sulfur with the alanyl moiety in
this type of ring system."

The rejection also indicates that the alleged equivalence of ring systems in Vincent et al corresponds to the disclosure of ring systems in applicants' parent application.

Applicants urge that the gist of their previous response with respect to Vincent et al was not understood. Applicants did not say that the penta[b]pyrrole ring system was not within the scope of the extremely broad disclosure of ring systems in Vincent et al, but rather that there was no specific disclosure or suggestion of penta[b]pyrrole ring systems which would lead one to believe that they had chemical or pharmacological properties equivalent to the isoquinolines or octahydroindoles specifically disclosed therein. However, even if the penta[b]pyrrole, octahydroindole, tetrahydroisoquinoline, etc. ring systems taken alone are considered to be equivalent based on the Vincent et al disclosure, applicants again urge that the Vincent et al compounds wherein a $-\overset{\text{O}}{\underset{\text{R}}{\text{C}}}-\text{CH}-(\text{CH}_2)_q-\text{Z}$ group is attached to the ring nitrogen are not equivalent to applicants' claimed compounds wherein a $-\overset{\text{O}}{\underset{\text{R}^3}{\text{C}}}-\text{CH}-\text{NH}-\overset{\text{R}^1}{\underset{\text{O}}{\text{C}}}-\text{CH}-\overset{\text{R}^2}{\underset{\text{O}}{\text{C}}}-\text{R}$ group is attached to the ring nitrogen. The best comparison would be for those compounds wherein Z is $-\text{NH}_2$, $\text{R}=\text{R}^3$ and q is zero, but there is still substantial difference between the resulting Vincent et al $-\text{NH}_2$ group and applicants' resulting $-\text{NH}-\overset{\text{R}^1}{\underset{\text{O}}{\text{C}}}-\overset{\text{R}^2}{\underset{\text{O}}{\text{C}}}-\text{R}$ group, and nothing in Vincent et al suggests applicants' substitution on the $-\text{NH}-$ group. As applicants have pointed out before, it is the compounds as a whole which must be considered, and the possible equivalence of one portion of each of two genres does not render one genus obvious over the other.

Hoefle et al (presumably U.S. Patent 4,344,949) is said to establish the equivalence of alanyl and sulfhydryl side chains, but applicants note that only tetrahydroisoquinoline

compounds are disclosed in U.S. Patent 4,344,949, and only octahydroindoles are disclosed in U.S. Patent 4,425,355. The fact that Hoefle et al have successfully pursued separate applications to two specific, different ring structures, i.e. isoquinolines and octahydroindoles, seems to underscore that it is not the nature of the side chain alone or the ring system alone which is responsible for activity, but rather that it is the nature of the compound as a whole which is important. The same reasoning - the unobviousness of the compound as a whole - applies to applicants' claimed aminoacyl-penta[b]pyrroles.

Applicants again urge that the combination of Vincent et al and Hoefle et al is improper. The reasoning for the combination appears to be as follows:

- (1) Sulfhydryl and aminoacyl side chains can be attached to an isoquinoline ring. (Hoefle).
- (2) Sulfhydryl and amino side chains can be attached to a variety of rings. (Vincent).
- (3) Therefore, aminoacyl side chains can be attached to a penta[b]pyrrole ring.

Applicants believe that to combine statements (1) and (2) to reach conclusion (3), there must be common ground in both statements and the conclusion. (1) and (2) do have sulfhydryl groups and isoquinoline groups in common, but neither of those groups is part of (3). One has to seize upon groups common to (1) and (2), then shift one's focus to an equivalent of each group, i.e. change sulfhydryl to aminoacyl and change isoquinoline to penta[b]pyrrole (which group is not specifically disclosed in nor suggested by the broad disclosure of the reference) and conclude that the new combination has the same activity as the previously disclosed compounds. There is no

suggestion in either reference, however, that angiotensin converting enzyme inhibitory activity will result if the structural formulae representing the two genres of reference compounds are each divided into parts, the common factors are eliminated, and a third genus is formed by selecting groups from the remaining structural parts. Using such a random selection process, one could just as easily decide to join an octahydroindole group to a penta[b]pyrrole group and expect activity. In the recent case Olsonite Corp. v. Bemis Mfg. Co., 226 USPQ 563 (CAFC, 1985), the court restated the test to be applied, i.e. whether the references considered individually or in combination disclose or suggest which of their elements should be discarded and which selected, modified and rearranged to produce the invention claimed. Neither Hoefle et al nor Vincent et al make any suggestions for choosing elements to arrive at the instant compounds.

While individual groups disclosed in the instant application, e.g. aminoacyl and penta[b]pyrrole, are known structural groups in the pharmaceutical/chemical arts in general and may be separately disclosed in the references in generic formulae representing antihypertensive compounds, there is no indication in the art that such groups may be successfully combined in a single molecule. It is not the individual differences between features of a claimed invention and the prior art which must be non-obvious, but the difference between the claimed invention as a whole and the prior art. Richdel Inc. v. Sunspool Corp., 219 USPQ 8 (CAFC, 1983). The fact that the cited references could be modified does not make applicants' invention obvious without the suggestion that such a modification be made. In re Gordon, 221 USPQ 1125 (CAFC, 1984).

Applicants urge that without benefit of their disclosure, the chances of arriving at aminoacyl-penta[b]pyrroles from the combination of Hoefle et al and Vincent et al is remote, and only appears obvious to the Examiner because of his liberal use of hindsight reconstruction. Hindsight is well known to be an improper basis for rejection.

Many cases can be cited against the use of hindsight: Stratoflex Inc. v. Aeroquip Corp., 218 USPQ 871 (CAFC, 1983), wherein it is said that the invention as a whole must have been obvious to one of ordinary skill in the art before it was made; Rosemount Inc. v. Beckman Instruments, Inc., 221 USPQ 1 (CAFC, 1984), wherein it was stated that one must go back in time to when the invention was made; Orthopedic Equipment Co., Inc., et al v. U.S. 217 USPQ 193 (CAFC, 1983), wherein it was held that one could not use the patent at issue to "guide through the maze" of the references, and wherein "Monday morning quarterbacking" was disapproved; and W. L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303 (CAFC, 1983) wherein the court states at page 313:

"It is difficult but necessary that the decision maker forget what he or she has been taught... about the claimed invention and cast the mind back to the time the invention was made..., to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art."

Applicants further suggest that the hindsight involved in this rejection not only results from consideration of the two references cited, but also from the many publications concerning ACE inhibitors which have appeared since the filing of the Vincent et al and Hoefle et al patents and instant application.

In fact, the subject matter of this case was originally part of an application that was considered allowable: the parent

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application was put into interference in September of 1983, and it was only in July of 1984 that the instant CIP application was filed. (A request to cancel penta[b]pyrroles from the parent was submitted in July, 1985.) While the art cited and overcome in the parent is not identical to that cited here, the gist of the rejections made and overcome in the parent is the same as in the instant application. Applicants suggest that this is another indication that hindsight is the basis for the instant rejection: if the instant compounds were allowable two years ago, why are they now rejected over art that is no more relevant? Just because those skilled in the art might now readily recognize that aminoacyl-penta[b]pyrrole compounds demonstrate antihypertensive activity (specifically, ACE inhibitor activity) does not mean that five years ago at the time of applicants filing their application, such a combination was obvious. Applicants' claims should not be rejected because they discovered first what others in the field now readily recognize.

Applicants urge that the cited references, alone or in combination, do not teach or suggest the combination of elements necessary to render the instant invention obvious. Only a fortuitous selection of elements from each case or a hindsight combination of the references could be said to render the compounds obvious. A serendipitous choice would not be the result of obviousness, and hindsight is well known to be an improper basis for rejection. Applicants respectfully request that the rejection of claims 1-30 be reconsidered, and all claims be allowed.

Respectfully submitted,

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